Message Pharmaceuticals, Inc. (formerly Symphony Pharmaceuticals)

RNA-Binding Protein Technology for Identification of New Drugs

During the 1990s, researchers were searching for the genetic basis for diseases and treatments. Symphony Pharmaceuticals aimed to develop compounds that could interact with a specific ribonucleic acid (RNA) to alter protein production. The company proposed to develop a screening technology that could test thousands of proteins and polypeptides to identify promising candidates to develop as drugs. Successful development would lead to finding small molecules that could stop disease processes at the sub-cellular level, thus preventing the expression of disease-related proteins. Their proposed research faced several challenges: the screening for a new drug is long and complex, Symphony had exhausted its funding sources, and no other company was attempting to develop this difficult new technology. In 1995, Symphony applied for and received Advanced Technology Program (ATP) funding for three years to further research and develop this technology.

During the course of the project, Symphony developed the Specific Control of RNA Interactions and Binding Events (SCRIBE) screening technology. SCRIBE spun off new research that attracted venture capital investment and Small Business Innovation Research (SBIR) awards from the National Institutes of Health. In 1997, Symphony merged with another biotechnology company, Cruachem Holdings, and became Bearsden Bio Inc., which continued to add to SCRIBE's testing compound library. Message Pharmaceuticals was spun off in late 1997 and attracted more SBIR funding and venture capital, which the company used to enhance the SCRIBE process in the post-project period. Although Message Pharmaceuticals and some licensees of SCRIBE screened thousands of compounds, they discovered no compounds that have yet advanced to clinical trials. The ATP-funded project and related research in the post-project period produced nine patents, eight publications, and sixteen presentations.

Message Pharmaceuticals suspended operations in early 2004. As of 2005, companies involved in RNA research were exploring other types of RNAs to look for RNA-binding proteins, especially to combat RNA viruses.

COMPOSITE PERFORMANCE SCORE
(based on a four star rating)

No Stars

Research and data for Status Report 95-01-0098 were collected during June – August 2005.

RNA Function Is Implicated in Diseases

Ribonucleic acid (RNA) is a molecule found in the nucleus and cytoplasm of each cell. It carries the cell's genetic template (instructions) to other parts of the cell where this template is converted into sequential orders of amino acids during protein synthesis. Proteins perform many tasks to keep the cell healthy, such as breaking down glucose for energy, building new proteins, allowing the cell to reproduce, breaking down waste, and fighting infection. Most human diseases involve protein abnormalities such as overproduction, underproduction, or a failure to function.

RNA-binding proteins bind to specific RNAs and control the type and quantity of protein that can be created in a cell. Because the production of certain proteins enables diseases to thrive, altering protein production would be

key to curing the targeted disease. By the mid-1990s RNA-binding proteins had been implicated in significant diseases; for example, amyloid precursor protein (APP) is associated with Alzheimer's disease and the rev protein is associated with HIV/AIDS. Thus, using RNA to alter protein expression (production) has broad therapeutic potential.

RNA-Binding Proteins Research: A Field in its Infancy

Symphony Pharmaceuticals, a young company with six employees, intended to develop a rapid assay tool to identify RNA-binding proteins that bind with certain sites on RNA. By identifying these RNA-binding proteins, researchers could determine the function of the interaction. The focus would be on APP, which appeared to be linked to Alzheimer's disease. The second phase of the project would demonstrate that new compounds could alter interactions between RNA-binding protein and RNA and change protein production. The third phase would discover functionally related genes by observing their interactions with a common RNA-binding protein and clone them. The assay tool would screen thousands of candidate compounds that could be purchased in "libraries" from commercial suppliers. High-volume screening would increase the chances of finding small-molecule candidates for development and testing against AIDS, Alzheimer's disease, cancer, and diabetes. At the time, a few companies had developed technologies for regulating the disease process at the RNA level, but successful licensing of these technologies to large pharmaceutical companies had not occurred. Furthermore, no companies had started the clinical trials required by the Food and Drug Administration for the approval of new drugs.

Because the production of certain proteins enables diseases to thrive, altering protein production would be key to curing the targeted disease.

If Symphony could develop a successful assay tool, the company would be able to exploit the niche market of RNA small-molecule research and advance the creation of novel drug agents through "rational" drug design, which tailors specific tests based on known chemical properties of selected proteins known as "targets." Quick and efficient assays would demonstrate the presence or absence of an RNA-binding protein for any gene. In particular, Symphony wanted to focus on regulating RNA-binding proteins functioning as "modulators" in the human brain, which play a specific role in promoting disease. If Symphony could discover ways to alter the action of known modulators, a cure might be found for central nervous system (CNS) diseases.

In pursuing high-risk RNA-binding protein research, Symphony was a pioneer; no other drug company was researching RNA-binding proteins, because the industry knew little about specific protein- and RNA-binding reactions. Symphony founder Maria Maccecchini and her research team had solicited several established drug development companies for collaborative funding, but the potential collaborators considered the research too high risk. Symphony was willing to invest in further research and recruited several scientists knowledgeable in RNA research to maximize the possibility of breakthroughs. The company applied for and received a three-year ATP cost-shared award to research RNA-binding proteins and find new drug candidates, which began in 1995.

If successful, the RNA-binding protein research would lead to a high-throughput process to test drug candidates as quickly as possible. Symphony intended to develop reasonably priced assay kits and license them to reagent companies, so that research in RNA-binding protein/RNA would increase. A high-throughput process would analyze thousands of samples per day.

Symphony Plans Research in Three Phases

Symphony first focused on assay development to measure protein synthesis in tissues. These assays would target a broad commercial market for identifying RNA-binding protein/RNA interactions that might apply to CNS diseases. The researchers were able to develop an affinity-based assay, which evaluated molecules based on attraction, but it was too expensive and inefficient.

In the project's next phase, Symphony used two methods in attempting to develop compounds that regulate specific RNAs. For the first method, the company bought and screened a wide variety of small-molecule libraries to discover drugs. The second method applied rational drug design principles to selected targets discovered in the screening processes.

Although Symphony tested thousands of compounds purchased from several commercial sources, they found no significant candidates for further research. Then, in 1997, molecular biologist and Symphony Research Vice President Tony Giordano and his team developed the Specific Control of RNA Interactions and Binding Events (SCRIBE) process. SCRIBE searched for small molecule mimics of complex biologicals, such as insulin. SCRIBE was intended to further narrow the target pool so that investigators could design tests on those targets based on the target's known chemistry and behavior. In designing SCRIBE, the team had used a rational drug-design process, which reduces the hit-or-miss nature of looking for new targets to those more likely to be "hits" for further drug candidate development.

SCRIBE started as a group of assays for which patents were filed as a result of the project research. With the development of SCRIBE, Symphony screened additional small molecules purchased from libraries such as those offered by ChemBridge. After screening more than 100,000 compounds, the researchers had not yet discovered any compounds which have advanced to the clinic. Symphony licensed the SCRIBE process to several drug and venture capital firms, such as Toucan Capital of Maryland and Boerhinger-Ingelheim of New Jersey, earning approximately $1 million. However, neither company discovered new drugs with SCRIBE.

In the third phase of the project, Symphony intended to develop RNA-binding protein cloning, followed by RNA cloning. This process would facilitate gene cloning for gene therapy, which replaces defective genes that cause such incurable CNS diseases as Alzheimer's. This phase was not completed because of insufficient progress in assay development and peptide screening.

Symphony employed two subcontractors who focused on RNA-binding proteins for specific diseases. James Malter, M.D., of the University of Wisconsin at Madison worked on an affinity cloning strategy for isolating RNA targets to a specific RNA-binding protein and to develop RNA-binding protein-based assays. Alan Frankel, Ph.D., of the University of California at San Francisco who had developed an HIV-based peptide screen worked on Alzheimer's disease and designed an RNA-binding peptide screen. No breakthroughs or discoveries were reported from the subcontractors' tasks.

Merger Results in Spinoff

In June 1997, Symphony merged with Cruachem Holdings to create Bearsden Bio Incorporated. The two companies were linked by their common involvement in RNA-based research and technology. The merger allowed Cruachem to expand its business by adding Symphony's two product lines, RNA molecules and the SCRIBE assay kit technology. Bearsden spun off Message Pharmaceuticals in December 1997 with the goal of perfecting the SCRIBE process, establishing partnerships with other pharmaceutical and biotechnology companies to test even more compounds, and eventually applying the technology to drug creation.

Symphony wanted to focus on regulating RNA-binding proteins functioning as "modulators" in the human brain, which play a specific role in promoting disease.

By 1998, Bearsden had received six Small Business Innovation Research (SBIR) awards totaling $1 million from the National Institutes of Health for spin-off work from the ATP-funded project. They used this funding to enhance SCRIBE and to continue research on various aspects of RNA and RNA-binding protein interaction related to infectious diseases, oncology, inflammatory diseases, and Alzheimer's disease. All the research projects aimed to develop orally bioavailable small molecules as alternatives to conventional large-molecule biopharmaceuticals. Bearsden also generated

new funding by issuing stock, but no new drug candidates resulted from this funding.

The research funded by ATP helped to establish RNA research as the state-of-the-art in drug discovery.

At the conclusion of the ATP-funded project in 1998, Bearsden was still doing related research, hoping to reduce the cost of the affinity-based assay, as well as the cost of the RNA used in the high-throughput assays. The company raised $6.3 million from five venture capital firms and attracted an additional $2.4 million in SBIR funding. In March 1999, as a separate company, Message received additional SBIR grants for research to understand the role RNA plays in reducing or eliminating tumors. The company hoped to discover small molecules that inhibit tumor growth during inflammation, but none have advanced to the clinic yet. No new molecules or drugs have resulted from this funding.

SCRIBE Generates License Income

Although the use of SCRIBE did not result in any new RNA-binding protein candidates for Message Pharmaceuticals or its licensees, it generated at least $1 million in licensing revenue for Message. The company used an RNA target or an RNA−protein interaction, but neither of these targets fit the conventional receptor or enzyme-based small-molecule drug discovery model. Giordano said this oversight was the chief reason that the company and SCRIBE's licensees had difficulty finding RNA-binding protein "hits" in the purchased screening libraries. More research is needed to find a family of hits against different RNA targets, he continued.

In early 2004, Message Pharmaceuticals went out of business. Although the SCRIBE process is no longer sold, the patents related to it reverted to SR-One, the venture capital arm of SmithKlineGlaxo, after Message's legal dissolution as a corporate entity was completed. In addition, the research funded by ATP helped to establish RNA research as the state-of-the-art in drug discovery. As a result, competitors have continued developing the technology. For example, by 2005, PTC Therapeutics, Inc. (PTC), a privately held biopharmaceutical company, was applying its integrated RNA biology and chemistry platforms to discover and develop small molecule drugs. PTC had success finding compounds affecting RNA-binding proteins by using more chemical approaches than Message, which had taken a primarily biological approach. PTC attracted more than $130 million in venture capital by late 2005 to support clinical development of PTC124, its drug to treat genetic disorders. Investments of this magnitude would not have been realized in 1995 because the industry did not fully accept RNA research until human genome mapping concluded in 2000. The ATP research set the stage for other companies to continue research.

Conclusion

Symphony Pharmaceuticals wanted to explore the drug potential of ribonucleic acid (RNA)-binding proteins in an attempt to make progress in the relatively unexplored field of RNA research. Toward that end, the company developed the Specific Control of RNA Interactions and Binding Events (SCRIBE) tool, a patented assay collection that resulted from their ATP-funded research. Although Symphony tested its tool against commercial peptide libraries during and after the project, no new clinical compounds targeting RNA-binding proteins were discovered, either by the company's testing or that of its licensees. Project designers attribute this failure to applying a traditional receptor/enzyme-molecule model to the more complex, less structured RNA molecular targets. Symphony became Bearsden Bio, Inc. in 1997.

The RNA-based technology received many Small Business Innovation Research grants from the National Institutes of Health, as well as funding from drug industry venture capital sources, and earned about $1 million from licensing fees. Bearsden spun off Message Pharmaceuticals at the end of 1997. Although the project and subsequent research resulted in nine patents, eight publications, and sixteen presentations, and generated licensing revenue, Message was unable to discover new drugs. Message closed its doors in 2004. However, as a result of this ATP-funded research that established RNA research as the state-of-the-art in drug discovery, other companies are continuing this research. As of 2005, new companies were involved in RNA-based research and were exploring other types of RNAs, some with their own proprietary SCRIBE-like technology.

PROJECT HIGHLIGHTS
Message Pharmaceuticals, Inc. (formerly Symphony Pharmaceuticals)

Project Title: RNA Binding Technology for Identification of Novel Therapeutics

Project: To develop assays and other molecular technologies to identify compounds that can regulate production of specific proteins, by intervening in the action of ribonucleic acid (RNA)-binding proteins, for the treatment of diseases, including central nervous system disorders, cancer, and viral infections.

Duration: 8/1/1995 - 7/31/1998
ATP Number: 95-01-0098

Funding (in thousands):

ATP Final Cost	$1,707	82.2%
Participant Final Cost	369	17.8%
Total	$2,076	

Accomplishments: Although Symphony Pharmaceuticals (later spun-off as Message Pharmaceuticals) did not achieve its project goals, it did develop the Specific Control of RNA Interactions and Binding Events (SCRIBE) process. The compounds discovered by SCRIBE have not yet advanced to clinical trials for Message Pharmaceuticals or its customers. SCRIBE did, however, earn about $1 million in licensing fees for Message Pharmaceuticals.

Message Pharmaceuticals received the following nine patents for technologies related to the ATP-funded project:

- "Universal method for detecting interactions between RNA molecules and RNA binding proteins" (No. 6,107,029: filed July 31, 1996, granted August 22, 2000)
- "RNA sequences which interact with RNA-binding proteins" (No. 5,859,227: filed February 20, 1997, granted January 12, 1999)
- "Method for identifying compounds affecting RNA/RNA binding protein interactions" (No. 6,004,749: filed July 31, 1997, granted December 21, 1999)
- "Method for identifying compounds RNA/RNA binding protein interactions" (No. 6,465,176: filed October 2, 1998, granted October 15, 2002)
- "Functional genomic screen for post-transcriptional 5' and 3' regulatory elements" (No. 6,448,007: filed June 23, 2000, granted September 10, 2002)
- "Bacterial RNase P proteins and their use in identifying antibacterial compounds" (No. 6,936,432: filed March 1, 2001, granted August 30, 2005)
- "Identification of compounds for the treatment or prevention of proliferative diseases" (No. 6,630,589: filed March 26, 2002, granted October 7, 2003)
- "Small molecule inhibitors of secretion of proteins encoded by ARE-mRNAs" (No. 6,872,850: filed April 8, 2002, granted March 29, 2005)
- "Inhibitors of RNase P proteins as antibacterial compounds" (No. 7,001,924: filed September 23, 2002, granted February 21, 2006)

Commercialization Status: Message Pharmaceuticals ceased operation in early 2004, and the SCRIBE process is no longer sold. The patents forming the foundation of SCRIBE will revert to SR-One, the venture capital arm of GlaxoSmithKline, when Message Pharmaceuticals completes its formal dissolution.

Outlook: The technology was discontinued when Message Pharmaceuticals ceased operations in 2004. No licensee has yet discovered new RNA-binding proteins using the SCRIBE technology. Competitors who continue the development may produce results in the future.

Composite Performance Score: No Stars

Number of Employees: 6 employees at project start, 0 as of June 2005.

Company:
Message Pharmaceuticals is no longer in existence.

Contact: Dr. Tony Giordano
Phone: (318) 675-7791

PROJECT HIGHLIGHTS
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Subcontractors:

- Dr. James Malter
  University of Wisconsin
  Madison, WI

- Dr. Alan Frankel
  University of California, San Francisco
  San Francisco, CA

- ChemBridge
  Glenview, IL

Publications:

- Bhattacharya, S., T. Giordano, G. Brewer, and J.S. Malter. "Identification of AUF-1 Ligands Reveals Vast Diversity of Early Response Gene mRNAs." *Nucl. Acids Res.* Vol. 27: pp. 1464-1472, 1999.

- Rogers, Jack T., Jeffrey D. Randall, Catherine M. Cahill, Paul S. Eder, Xudong Huang, Hiromi Gunshin, Lorene Leiter, Jay McPhee, Satinder S. Sarang, Tada Utsuki, Nigel H. Greig, Debomoy K. Lahiri, Rudolph E. Tanzi, Ashley I. Bush, Tony Giordano, and Steve R. Gullans. "Identification of AUF-1 Ligands Reveals Vast Diversity of Early Response Gene mRNAs." *Nucleic Acids Research*, Vol. 27, No. 6: pp.1,464-1,472, 1999.

- Xavier, K.A., P.S. Eder, and T. Giordano. "RNA as a Drug Target: Methods for Biophysical Characterization and Screening." *Trends in Biotechnology*, Vol. 18: pp. 349-356, 2000.

- Pillutla, R., K. Hsiao, R. Brissette, P. Eder, T. Giordano, P. Fletcher, M. Lennick, A. Blume, and N. Goldstein. "A Surrogate-Based Approach for Post-Genomic Partner Identification." *BMC Biotechnology*, Vol. 1: p. 6, 2001.

- Rogers, Jack T., Jeffrey D. Randall, Paul S. Eder, Xudong D. Huang, Ashley I. Bush, Rudolph E. Tanzi, A. Venti, S. M. Payton, Tony Giordano, S. Nagano, C. M. Cahill, R. Moir, Debomov K. Lahiri, Nigel H. Greig, Satinder S. Sarang, and Steve R. Gullans. "Alzheimer's Disease Drug Discovery Targeted to the APP mRNA 5' Untranslated Region." *Journal of Molecular Neuroscience*, Vol. 19, No. 1-2: pp. 77-82, August-October 2002.

- Rogers, Jack T., Jeffrey D. Randall, Catherine M. Cahill, Paul S. Eder, Xudong Huang, Hiromi Gunshin, Lorene Leiter, Jay McPhee, Satinder S. Sarang, Tada Utsuki, Nigel H. Greig, Debomoy K. Lahiri, Rudolph E. Tanzi, Ashley I. Bush, Tony Giordano, and Steve R. Gullans. "An Iron-responsive Element Type II in the 5'-Untranslated Region of the Alzheimer's Amyloid Precursor Protein Transcript." *The Journal of Biological Chemistry*, Vol. 277, No. 47: pp. 45,518–45,528, November 22, 2002.

- Greig, Nigel H., Tony Giordano, Xiaoxiang Zhu, Qian-sheng Yu, Tracy Ann Perry, Harold W. Holloway, Arnold Brossi, Jack T. Rogers, Kumar Sambamurti, and Debomoy K. Lahiri. "Thalidomide-based TNF-a Inhibitors for Neurodegenerative Diseases." *ACTA Neurobiologiae Experimentalis*, Vol. 64: pp. 1-9, 2004.

- Utsuki, T., Q.S. Yu, D. Davidson, D. Chen, H. Holloway, K. Sambamurti, D. Lahiri, N. Greig, and T. Giordano. "Identification of Novel Small Molecule Inhibitors of APP Protein Synthesis as a Route to Lower Alzheimer's Disease Amyloid-□ Peptide." *J. Pharmacology . Experimental Therapeutics*, in press, 2006.

Presentations:

- Speaker, Communitech Conference, 1997

- Panelist, Delaware Valley Biotechnology Association, 1997

- Poster session, American Society for Biochemistry and Molecular Biology (ASBMB) Conference, 1997

- Panelist, Pennsylvania Biotech Association, 1998

- Talk, Maryland Biotechnology Partnership Conference, 1998

- Poster session, Proteins that Bind RNA Meeting, 1998

- Poster session, ASMBM Meeting, 1998

- Poster session, RNA Society Meeting, 1998

PROJECT HIGHLIGHTS
Message Pharmaceuticals, Inc. (formerly Symphony Pharmaceuticals)

- Pharmaceutical and Bioanalytical Analysis meeting, 1998
- Panelist, Pennsylvania Biotech Association, 1999
- Talk, Drug Disovery Conference, 2000
- Talk, China Drug Discovery Conference, 2001
- Talk, RNA Society Meeting, 2001
- Talk, Knowledge Foundation RNA Conference, 2001
- Poster, Knowledge Foundation RNA Conference, 2002
- Talk, Knowledge Foundation RNA Conference, 2002